REMARKS

Applicants thank the Examiner for the review of the instant application and acknowledgment of Applicants' request for correction of inventorship. Claims 4-17 are presented for examination. For the reasons stated below, Applicants respectfully traverse the rejection of the pending claims.

Priority

The PTO asserts that because the disclosure of PCT/US00/23328 is not enabling for the instant invention, the priority date of the application is filing date of the present application, May 2, 2002.

Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 3, 2002. Applicants submit that for the reasons stated herein, the claimed polypeptides are enabled by the disclosure of PCT/US00/23328 and have a credible, substantial, and specific utility. Applicants maintain that the present application is entitled to at least the priority date of August 24, 2000.

Rejection Under 35 U.S.C. §101

The PTO maintains its rejection of Claims 4-17 under 35 U.S.C. § 101 as lacking utility for the reasons set forth in the previous Office Action. The PTO asserts that "[g]iven the increase in message (cDNA) for PRO1277 in esophageal and melanoma tumor compared to normal esophageal and skin tissue counterparts, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that a more highly expressed mRNA would directly correlate with increased polypeptide levels. Further research needs to be done to determine whether the increase of PRO1277 cDNA... supports a role for the polypeptide in the cancerous tissue; such a role has not been suggested by the instant disclosure." *Office Action* at 5 (emphasis in original). The PTO relies on Hu *et al.*, Haynes *et al.*, Chen *et al.* and Gygi *et al.* for the propositions that the literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue, and that the correlation between mRNA expression and protein expression is poor at best. The PTO also states that declarations and supporting references submitted with Applicants' previous response are insufficient to overcome the rejection.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." *M.P.E.P.* § 2107.01 (emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "to violate § 101 the claimed device must be totally incapable of achieving a useful result." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 U.S.P.Q.2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent

examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys" the PTO must establish that it is "more likely than not that one of ordinary skill in the art would doubt (i.e., 'question') the truth of the statement of utility." *M.P.E.P.* § 2107.02 III A. The M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained [] because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**. *M.P.E.P.* § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a

> whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. *M.P.E.P.* at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is "an invariable exact correlation" between gene expression and protein expression. Instead, Applicants' position detailed below is that a measured change in gene expression in cancer cells establishes a "significant probability" that the expression of the encoded polypeptide in cancer will also be changed based on "a reasonable correlation therebetween."

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed polypeptides have utility as diagnostic tools for cancer, particularly esophageal and skin cancer. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1277 polypeptide is expressed at least two-fold higher in normal esophageal and skin tissue compared to esophageal and melanoma tumor tissue, respectively, and the PTO has accepted that PRO1277 nucleic acids have utility and are enabled as diagnostic tools;

2. Applicants assert that it is well-established in the art that a **change** in the level of mRNA for a particular protein, e.g. a decrease, generally leads to a corresponding **change** in the level of the encoded protein, e.g. a decrease;

3. Given Applicants' evidence that the level of mRNA for the PRO1277 polypeptide is decreased in esophageal and melanoma tumor tissue compared to normal esophageal and skin tissue, respectively, it is likely that the PRO1277 polypeptide is also decreased in esophageal and melanoma tumor tissue compared to normal esophageal and skin tissue, respectively. Polypeptides such as PRO1277 which are differentially expressed in certain cancers are useful as diagnostic tools.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO cites Hu *et al.* to support its assertion that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue;

2. The PTO cites Haynes *et al.*, Chen *et al.* and Gygi *et al.* for the proposition that the correlation between mRNA expression and protein expression is poor at best; and

3. The PTO concludes that based on the cited literature, one skilled in the art would not assume that a more highly expressed mRNA would directly correlate with increased polypeptide levels. Therefore, further research needs to be done to determine if the increase or decrease in PRO1277 DNA supports a role for the peptide in cancerous tissue.

As detailed below, Applicants submit that the PTO has failed to demonstrate that this is one of the "rare cases" where the applicants have "asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." *M.P.E.P.* § 2107.02 III B. First, Applicants submit that the Hu *et al.*, Haynes *et al.*, Chen *et al.* and Gygi *et al.* references are not contrary to Applicants' arguments, and therefore are not evidence to support the PTO's position. Second, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Applicants have established that the Gene Encoding the PRO1277 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

As an initial matter, Applicants address the PTO's statement that "[t]he Office acknowledges that the microarray experiments disclosed in the specification (example 18) does measure the level of mRNA expressed in tumor and normal controls." *Office Action* at 3. Applicants would like to clarify that Example 18 used quantitative PCR analysis of a cDNA library to measure mRNA expression, not a microarray analysis. While the distinction does not matter with respect to the PTO's statements regarding the relevance of the Pennica *et al.* and Sen *et al.* references, Applicants would like to clarify this point for the record.

Appellants note that in the closely related application Serial No. 10/063,688, directed to nucleic acids related to SEQ ID NO:33 which encodes the PRO1277 polypeptide, the PTO has acknowledged that the nucleic acids have utility. *See Office Action dated 9/15/2005* at 2. In that case, the exact same data from Example 18 was relied on for utility of the claimed nucleic acids as diagnostic tools for esophageal and melanoma tumors. In response to Applicants' arguments, the PTO stated "Applicants assertion that the differentially expressed message can be used as a diagnostic tool for stomach and lung [*sic*] tumors is found to be persuasive." *Id.* at 2 (emphasis added). Therefore, Applicants submit that the PTO's questions regarding the significance of the exact same data in the instant case are moot in light of this statement.

In spite of the PTO's admission that the data in Example 18 are sufficient to provide utility for the nucleic acids encoding PRO1277 polypeptide, Applicants next turn to the PTO's arguments based on Hu *et al.* (J. Proteome Res., 2(4):405-12 (2003)) that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. *See Office Action* at 9, 10 and 12.

In Hu, the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a *known* role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a *published* role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a *published* or *known* role for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's results merely reflect a bias in the literature toward studying the most prominent targets, and reflect nothing regarding the ability of a gene that is 2-fold or more differentially expressed in tumors to serve as a disease marker.

Hu acknowledges the shortcomings of this method in explaining the disparity in Hu's findings for ER-negative versus ER-positive tumors: Hu attributes the "bias in the literature" toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression levels in less-prevalent (and, therefore, less studied) ER-negative tumors. *Id.* Because of this intrinsic bias, Hu's methodology is unlikely to

ever note a correlation of a disease with less differentially-expressed genes and their corresponding proteins, regardless of whether or not an actual relationship between the disease and less differentially-expressed genes exists. Accordingly, Hu's methodology yields results that provide little or no information regarding biological significance of genes with less than 5-fold expression change in disease. Nowhere in Hu does it say that a lack of correlation in their study means that genes with a less than five-fold change in level of expression in cancer cannot serve as a molecular marker of cancer.

In response to similar arguments by Applicants in their previous response, the PTO states that:

> Contrary, to Applicants assertion that Hu et al.'s methodology provide little or no information regarding biological significance of genes with less than 5-fold expression change in disease, the reference teaches that "careful hunt for corroborating evidence of a role in breast cancer should precede any further study of genes with less than 5-fold expression level change". *Office Action* at 6.

Applicants submit that this does not address the main point of Applicants' previous arguments as elaborated above. Applicants are not relying on any "role" that PRO1277 has in cancer for their asserted utility. Instead, Applicants are relying on the differential expression of PRO1277 in certain tumors compared to their normal tissue counterparts. Nowhere in Hu does it say that a lack of correlation in their study means that genes with a less than five-fold change in level of expression in cancer cannot serve as a molecular marker of cancer.

A lack of known role for PRO1277 in cancer does not prevent its use as a diagnostic tool for cancer. There is a difference between use of a gene for distinguishing between tumor and normal tissue on the one hand, and establishing a role for the gene in cancer on the other. Genes with lower levels of change in expression may or may not be the most important genes in causing the disease, but the genes can still show a consistent and measurable change in expression. While such genes may or may not be good targets for further research, they can nonetheless be used as diagnostic tools. Thus, Hu does not refute the Applicants' assertion that the PRO1277 gene can be used as a cancer diagnostic tool because it is differentially expressed in certain tumors, and the PTO's response quoted above does not address Applicants' arguments.

In addition, the PTO's own written policies recognize that the utility of a nucleic acid does not depend on the function of the encoded gene product. The Utility Examination

Guidelines published on January 5, 2001 state: "the utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have a specific and substantial utility because, e.g. it hybridizes near a disease-associated gene or it has a gene regulating activity." (Federal Register, Volume 66, page 1095, Comment 14); *see also Exhibits 1-3* attached hereto (U.S. Patent Nos. 6,465,185, 6,228,582, and 6,162,604) (patents on polymorphisms which are indicative of a predisposition to a particular condition are patentable even though they may or may not cause the disease itself). Similarly, here the disclosed nucleic acids, as well as the encoded polypeptides and related antibodies, are useful for determining whether an individual has cancer regardless of whether or not they are the cause of the cancer.

The position of the PTO requiring a known role for PRO1277 in cancer for utility is also inconsistent with the analogous standard for therapeutic utility of a compound where "the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an 'immediate benefit to the public' and thus satisfies the utility requirement." M.P.E.P. §2701.01 (emphasis original). Here, the mere identification of altered expression in tumors is relevant to diagnosis of tumors, and, therefore, provides an immediate benefit to the public.

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration previously submitted, establish that there is at least a two-fold difference in PRO1277 cDNA between esophageal and melanoma tumor tissue compared to normal esophageal and skin tissue, respectively. Therefore, it follows that expression levels of the PRO1277 gene can be used to distinguish esophageal and melanoma tumor tissue from normal esophageal and skin tissue, respectively. The PTO has not offered any significant arguments or evidence to the contrary, and this is the same assertion that Applicants have made and the PTO has accepted in the related application, Serial No. 10/063,688, directed to nucleic acids related to SEQ ID NO:33 which encodes the PRO1277 polypeptide. *See Office Action dated 9/15/2005* at 2.

As Applicants explain below, it is more likely than not that the PRO1277 polypeptide can also be used to distinguish esophageal and melanoma tumor tissue from normal esophageal and skin tissue, respectively.

Applicants have established that the Accepted Understanding in the Art is that there is a Positive Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a **change** in the level of mRNA for a particular protein, generally leads to a corresponding **change** in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1277 polypeptide in esophageal and melanoma tumor, it is likely that the PRO1277 polypeptide is differentially expressed; and proteins differentially expressed in certain tumors have utility as diagnostic tools.

In response to Applicants' assertion, the PTO cites Haynes *et al.* (Electrophoresis, 19(11):1862-71 (1998)), Chen *et al.* (Mol. and Cell. Proteomics, 1:304-313 (2002)), and Gygi *et al.* (Mol. and Cell. Bio., Mar. 1999, 1720-1730) as support for its argument that "the correlation between mRNA expression and protein expression is poor at best." *Office Action* at 10. For the reasons discussed previously, and reiterated below, Haynes, Chen, and Gygi are not contrary to Applicants' asserted utility.

Haynes studied whether there is a correlation between the level of mRNA expression and the level of protein expression for 80 selected genes from yeast. The genes were selected because they constituted a relatively homogeneous group with respect to predicted half-life and expression level of the protein products. *See* Haynes at 1863. Haynes did not examine whether a **change** in transcript level for a particular gene led to a **change** in the level of expression of the corresponding protein. Instead, Haynes determined whether the steady-state transcript level correlated with the steady-state level of the corresponding protein based on an analysis of 80 different genes.

Haynes reported to have "found a general trend but no strong correlation between protein and transcript levels." *Id.* However, a cursory inspection of Fig. 1 shows a clear correlation between the mRNA levels and protein levels measured. This correlation is confirmed by an inspection of the full-length research paper from which the data in Fig. 1 were derived, (Gygi *et al.*, Molecular and Cellular Biology, Mar. 1999, 1720-1730, previously submitted as Exhibit 2). Gygi states that "there was a general trend of increased protein levels resulting from increased mRNA levels," with a correlation coefficient of 0.935, indicating a strong correlation. Gygi at 1726. Moreover, Gygi also states that the correlation is especially strong for highly expressed

mRNAs. *Id.* Thus, it is not clear that Haynes even supports the Examiner's position, as Haynes did report a general trend, and Gygi reports a strong correlation between increasing mRNA levels and increasing protein levels.

The PTO focuses on the portion of Haynes where the authors reported that for some of the studied genes with equivalent mRNA levels, there were differences in corresponding protein expression, including some that varied by more than 50-fold. Similarly, Haynes reports that different proteins with similar expression levels were maintained by transcript levels that varied by as much as 40-fold. *Id.* Thus, Haynes showed that for one type of yeast, similar mRNA levels for *different* genes did not universally result in equivalent protein levels for the *different* gene products, and similar protein levels for *different* gene products did not universally result from equivalent mRNA levels for the *different* genes. These results are expected, since there are many factors that determine translation efficiency for a given transcript, or the half-life of the encoded protein. Not surprisingly, based on these results, Haynes concluded that protein levels cannot always be accurately predicted from the level of the corresponding mRNA transcript *when looking at the level of transcripts across different genes.*

Importantly, Haynes did not say that for a single gene, the level of mRNA transcript is not positively correlated with the level of protein expression. Applicants have asserted that increasing or decreasing the level of mRNA for the same gene leads to a increase or decrease for the corresponding protein. Haynes did not study this issue and says absolutely nothing about it. Therefore, Haynes is not inconsistent with or contradictory to the utility of the instant claims, and offers no support for the PTO's position.

The PTO also cites Chen *et al.* for support for the assertion that polypeptide levels cannot be accurately predicted from mRNA levels. In Chen, the authors examined the relationship between mRNA levels and protein levels in 76 lung adenocarcinomas and 9 non-tumor lung samples. Like Haynes, Chen examined the global relationship between mRNA and the corresponding protein abundance by calculating the average mRNA and protein level of all the samples for each gene or protein, and then looked for a correlation across different genes. As discussed above with respect to Haynes, this measurement of a correlation across genes is not relevant to Applicants' asserted utility. Chen also looked at the level of mRNA of 98 individual

genes and their corresponding proteins across the samples. Chen reports that 21.4% (21 of 98) of the genes showed a statistically significant correlation between protein and mRNA expression.

Chen provides scant evidence to counter Applicants' asserted utility for the claimed antibodies because portions of Chen support Applicants' assertions, and the remaining portions provide little insight into the relationship between mRNA levels and corresponding protein levels for mRNA that is differentially expressed in tumor cells relative to normal cells. Rather than looking for mRNAs which were differentially expressed, Chen merely selected proteins whose identity could be determined regardless of any changes in expression level (Chen at 306, right column). Importantly, it is not known if there was any substantial difference in mRNA levels for the various genes across samples – in short, with the exception of the genes in Figures 2A-2C, it is not known if the genes examined were differentially expressed. Also of significance for Applicants' asserted utility is the fact that Chen did not attempt to examine any differential expression between the cancerous lung samples and the non-cancerous lung samples – Chen did not distinguish between cancer and normal samples in their analysis.

Applicants have asserted that changes in mRNA levels, particularly those which are two-fold or greater, will correspond with measurable changes in polypeptide expression. The data in Chen support Applicants' assertion. In Figures 2A-2C, Chen plots mRNA value vs. protein value for three genes. In these figures, a wide range of mRNA expression levels were observed (approximately seven- to eight-fold), and a correlation between mRNA and protein levels was observed for all three mRNA/protein pairs. This supports Applicants' asserted correlation between changes in mRNA levels which are two-fold or greater and changes in polypeptide expression.

The PTO relies on the fact that Chen also reports a lack of correlation for some mRNA/protein pairs to support its assertion that polypeptide levels cannot be accurately predicted from mRNA levels. However, the lack of correlation reported by Chen could be a result of a lack of substantial changes in mRNA level. This can be understood by again turning to Figures 2A-2C. As noted above, where a wide range of mRNA expression levels are seen, a correlation between mRNA and protein levels was observed. However, if one examines the data points within a small range of mRNA levels for these same genes, e.g. 500-600 or 5000-6000 in Figs. 2A-2C, it is clear that a correlation would not be detected for the data within this range.

This does not mean that a correlation between changes in mRNA and protein does not exist for these genes, as is evident when larger changes in mRNA expression are included in the analysis. Instead, this indicates that for relatively small changes in mRNA, any correlation is masked by imprecision in the measurements.

Chen's experiment compared mRNA levels vs. protein levels across samples without selecting mRNA that showed a difference in expression level. And unlike Applicants, Chen did not examine differences in mRNA between tumor and normal tissue. Since almost all samples tested by Chen were from the same type of tissue, few substantial variations in the level of mRNA or protein for a particular gene across the samples tested would be expected. Instead, it would be expected that most genes examined by Chen would have similar mRNA or protein levels across the samples. Figures 2A-2C of Chen demonstrate that the methods utilized by Chen cannot detect correlations between mRNA and protein levels when only small differences in mRNA expression are observed, but a correlation is detected when larger differences in mRNA expression are observed.

Accordingly, the only data reported by Chen which shows substantial changes in the expression of mRNA, Figures 2A-C, confirms Applicants' assertion that substantial changes in mRNA levels (e.g., 2-fold or greater) will correspond to substantial changes in polypeptide expression. Further, this data also explains the lack of observed correlation between mRNA levels and protein levels for other genes reported by Chen. Thus, even given Chen's inability to detect a correlation between mRNA and protein in some genes, Chen's results do not refute Applicants' position.

Instead, Chen supports Applicants' position that a significant correlation between mRNA and protein levels exists for changes in mRNA levels that are 2-fold or greater. In further support of Applicants' position, Chen cites Celis *et al.* (FEBS Lett., 480:2-16 (2000)) stating that the authors "found a good correlation between transcript and protein levels among 40 well resolved, abundant proteins using a proteomic and microarray study of bladder cancer." *Chen* at 311, first column (emphasis added). As mentioned above, the lack of a correlation across genes is not relevant to Applicants' asserted utility, and therefore Chen's discussion of this issue and citation of Anderson and Seilhamer (Electrophoresis, 18:533-37 (1997)) and Gygi *et al.* (Mol. Cell. Bio., 19:1720-30 (1999)) offer no support for the PTO's position.

Even if the results in Chen supported the PTO's argument, which they do not as discussed above, one contrary example does not establish that one of skill in the art would find it is more likely than not there is no general correlation between changes in mRNA level and changes in protein level for an individual gene. There are other non-transcriptional mechanisms for regulating gene and protein expression (*i.e.*, post-transcriptional regulation of genes, translation efficiency, etc.). However, as shown by the declarations, references, and textbooks discussed below, Applicants submit that the understanding in the art is that generally there is a correlation between a change in mRNA level and a change in protein level. In fact, the working hypothesis among those skilled in the art, as illustrated by the evidence presented by Applicants, is that there is a positive correlation between **changes** in mRNA levels and **changes** in protein levels for a particular gene.

In response to Applicants' arguments, the PTO has stated that:

> Contrary, to Applicants['] assertion that Haynes et al. does not contradict the utility and enablement of the instant claims (page 18 of the response), Haynes et al. states that "These results suggests that even for a population of genes predicted to be relatively homogeneous wit[h] respect to protein half-life and gene expression, the protein levels cannot be accurately predicted from the level of the corresponding mRNA" (page 1863, 2nd paragraph). Although, Applicants assert that there is a strong correlation between mRNA expression, Gygi et al. conclude that transcript levels provide little predictive value with respect to the extent of the protein expression (page 1730, last line). *Office Action* at 6.

Applicants respectfully submit that these arguments are not responsive to Applicants' main point regarding deficiencies of Haynes and Gygi – both references looked at static levels of mRNA across different genes not changes in the level of expression for a single gene. Therefore, when Haynes and Gygi state that protein levels cannot be accurately predicted from the level of the corresponding mRNA, they are referring only to the static level of mRNA. Applicants have not asserted that protein levels can be predicted from static levels of mRNA, and the asserted utility does not depend on there being a correlation between static levels of mRNA and protein across different genes. Instead, Applicants have asserted that **changes** in mRNA level for an individual gene are generally correlated with **changes** in the level of the encoded protein. Applicants have asserted that because there is a change in the level of mRNA for PRO1277 in esophageal and melanoma tumors compared to their normal tissue counterparts, the level of PRO1277 protein will show a similar change. Predicting the absolute level of protein from the

static level of mRNA is not required for this asserted utility since it is the change in the level of mRNA and protein that is important. Haynes and Gygi have absolutely no bearing on this issue since they examined static levels of mRNA for different genes.

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also previously submitted a copy of the declaration of Paul Polakis, Ph.D., an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, **including the data discussed in paragraphs 4 and 5 above** [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of

the Cell (3rd ed. 1994) (previously submitted as Exhibit 3, herein after Cell 3rd) and (4th ed. 2002) (previously submitted as Exhibit 4, herein after Cell 4th)). Figure 9-2 of Cell 3rd shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Cell 3rd provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Cell 3rd at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Cell 3rd at 453 (emphasis added). Thus, as established in Cell 3rd, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Cell 4th, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Cell 4th at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Cell 4th illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Cell 4th at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Cell 4th at 379 (emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (previously submitted as Exhibit 5) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, previously submitted as Exhibit 6. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis

and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" Zhigang at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Zhigang at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." *Id.* at 7

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), previously submitted as Exhibit 7, states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein. The PTO has not submitted any significant evidence to the contrary.

In response to the second Grimaldi Declaration, the PTO focuses on paragraph 4 of the declaration where he states that for chromosomal aberrations which result in aberrant expression of a mRNA and corresponding protein, "the gene product is a promising target for cancer therapy, for example, by the therapeutic antibody approach." *Office Action* at 8 (emphasis added). The PTO rejects this argument, stating that unlike Her2/Neu and t(5;14), the PRO1277 gene has not been associated with tumor formation of the development of cancer, and no translocation of the PRO1277 gene is known to occur. The PTO concludes that "in the absence of any of the above information, all the that specification does is present evidence that the mRNA

encoding PRO1277 is more highly expressed in an unknown number of samples, and invite the artisan to determine the rest of the story." *Office Action* at 8.

Applicants submit that the PTO's argument is not responsive to Applicants' previous arguments as reiterated above. Applicants did not rely on paragraph 4 of the second Grimaldi declaration which discusses targets for cancer therapy. Instead, Applicants relied on his statements in paragraph 5 discussing the fact that it is well established that increases or decreases in mRNA generally lead to corresponding increases or decreases in the encoded protein, and that techniques which measure mRNA would have little value and not be so widely used if there were no correlation between the two. The PTO fails to respond to this argument.

In addition, as stated previously, a lack of known role for PRO1277 in cancer does not prevent its use as a diagnostic tool for cancer. The fact that there is no known translocation or mutation of PRO1277, for example, is irrelevant to whether its differential expression can be used to assist in diagnosis of cancer – one does not need to know why PRO1277 is differentially expressed, or what the consequence of the differential expression is, in order to exploit the differential expression to distinguish tumor from normal tissue. In fact the Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer have utility. (*See* the caveat in Example 12 which state that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin and antibodies against the protein can be used to diagnose cancer.) In addition, while Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO has issued several patents claiming differentially expressed polypeptides and antibodies to the same, or methods employing such antibodies. (*See, e.g.,* U.S. Patent No. 6,414,117, U.S. Patent No. 6,124,433, U.S. Patent No. 6,156,500, and U.S. Patent No. 6,562,343 previously submitted as Exhibits 8-11.)

Similarly, in response to the Polakis declaration, the PTO states that the specification describes only mRNA expression data, that it is not known whether PRO1277 polypeptide is expressed in normal esophageal and skin tissue, and that "[t]here is no nexus between the mRNA expression and PRO1277 polypeptide." *Office Action* at 9. The PTO concludes that the disclosure of differential mRNA expression in Example 18 is an invitation to experiment,

quoting paragraph 7 of the first Grimaldi declaration "additional studies can then be conducted if further information is desired." *Office Action* at 9.

These arguments are not responsive to Applicants' arguments. While it is true that Example 18 only describes mRNA expression data, there is an obvious nexus between changes in PRO1277 mRNA and the PRO1277 polypeptide. First, the PRO1277 mRNA encodes the PRO1277 protein. Second, as described in numerous references and declarations above, regulation of mRNA is the primary method for controlling the expression of a gene, and there is a general correlation between changes in mRNA levels and changes in protein levels. No additional experimentation is needed to establish that it is more likely than not that the claimed polypeptides can be used as diagnostic tools for cancer, particularly esophageal and skin cancer.

The PTO's reliance on the quote from the first Grimaldi declaration is clearly misplaced when read in context:

> 7. The results of the gene expression studies indicate that the genes of interest can be used to differentiate tumor from normal. The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue. ...**If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor.** Additional studies can then be conducted if further information is desired. *First Grimaldi Declaration* at ¶ 7 (emphasis added).

It is obvious that Mr. Grimaldi was stating that it is his expert opinion that the information provided in Example 18 is sufficient to use the gene, protein and antibody as diagnostic tools, and that no further testing or information is required. However, if additional information is desired, such as the role of the gene or protein in cancer formation or growth, additional studies can be conducted. It is disingenuous of the PTO to take this quote out of context to suggest that Mr. Grimaldi is stating that further research is required to use the claimed invention when the remainder of his declaration is clearly stating otherwise.

Finally, Applicants turn to the PTO's discussion of the Applicants' supporting references. The PTO acknowledges the submission of two Alberts references, as well as the Lewin, Zhigang, and Meric references. *See Office Action* at 11. However, the PTO only responds to the Meric reference, essentially ignoring the remaining references. The PTO states that Meric teaches that

gene expression is complicated, and regulated at numerous levels, and that changes in mRNA sequences increase or decrease translation efficiency. *Office Action* at 11-12.

These arguments are not responsive to Applicants' argument that Meric teaches that "[t]he fundamental principal of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer and normal cells." *Meric* at 971. Meric does teach that mutations of genes as well as alternate splicing and alternate transcription start sites can lead to altered translation efficiency in certain cancer cells. *Id.* at 973-974. As support, Meric cites three examples of point mutations, and four examples of alternate splicing. *Id.* at 974. However, the PTO has not shown, and there is no evidence, that the PRO1277 mRNA is either mutated, alternately spliced, or has an alternate transcription start site. Nor has the PTO established that point mutations or alternate splice variants leading to changes in translation efficiency are common in cancer, or common in esophageal or melanoma tumors in particular. These few examples are not sufficient to provide evidence that one skilled in the art would reasonably doubt Applicants' asserted utility, or reject the teaching of Applicants' supporting references and declarations.

Applicants have already acknowledged that gene expression is regulated at numerous levels. However, as the supporting references and declarations Applicants have supplied make clear, regulation of mRNA levels is the predominant mechanism of control for the majority of genes. Meric supports this assertion because "[t]he **fundamental principle** of molecular therapeutics in cancer is to exploit the **differences** in gene expression between cancer cells and normal cells." Meric *et al.* at 971 (emphasis added). The only reason mRNA is of any interest in studying the mechanism of cancer formation and growth is because mRNA encodes protein. If there were no general correlation between differences in mRNA and differences in protein, there would be no reason to study changes in mRNA.

In summary, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1277 mRNA is more highly expressed in normal esophageal and skin tissue compared to esophageal and melanoma tumor, respectively, the PRO1277 polypeptide will also be more highly expressed in normal esophageal and skin tissue compared to esophageal and melanoma tumor, respectively.

This differential expression of the PRO1277 polypeptide makes it useful as a diagnostic tools for cancer, particularly esophageal and melanoma cancer.

The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

Applicants remind the PTO that the M.P.E.P. cautions that rejections for lack of utility are rarely sustained by federal courts, and that generally speaking, a utility rejection was sustained because the applicant asserted a utility "that could **only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art.**" M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis

in original, bold emphasis added). Rather than being wholly inconsistent with contemporary knowledge in the art, Applicants' asserted utility is squarely within the teaching of leading textbooks in the field, and is supported by references and the declarations of skilled experts.

The PTO has failed to offer any arguments or cite any references to establish "that one of ordinary skill in the art would reasonably doubt" that polypeptides differentially expressed in certain tumors can be used as a diagnostic tool. Hu *et al.*, Haynes *et al.*, Gygi *et al.*, and Chen *et al.* do not support the PTO's position and are not contrary to Applicants' asserted utility. Likewise, the PTO has not offered any substantial arguments or evidence to rebut the numerous declarations and references Applicants' have submitted in support of their asserted utility. Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed polypeptides can be used as diagnostic tools for cancer, particularly esophageal and skin cancer.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Polypeptides

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed polypeptides related to PRO1277. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1277 gene and polypeptide in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed polypeptides.

As discussed above, there are significant data which show that the gene for the PRO1277 polypeptide is expressed at least two-fold higher in normal esophageal and skin tissue compared to esophageal and melanoma tumor, respectively. These data are strong evidence that the PRO1277 gene and polypeptide are associated with esophageal and melanoma tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence

associating the PRO1277 gene and polypeptide with a specific disease. The asserted utility for the claimed polypeptides as diagnostic tools for cancer, particularly esophageal and melanoma tumor, is a specific utility – it is not a general utility that would apply to the broad class of polypeptides.

Conclusion

The PTO has asserted two arguments to support its conclusion that based on the cited literature, one of skill in the art would not assume that higher expression of mRNA would correlate with increased polypeptide levels: (1) the PTO cites Hu *et al.* to support its position that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue; and (2) the PTO cites Haynes *et al.*, Gygi *et al.*, and Chen *et al.* to support its assertion that mRNA levels are not predictive of protein levels. The PTO states that further research needs to be done to determine if the increase or decrease in PRO1277 DNA supports a role for the peptide in cancerous tissue. Applicants have addressed each of these arguments in turn.

First, the Applicants provided a first Declaration of Chris Grimaldi stating that the gene expression data in Example 18 are real and significant. This declaration also indicates that given the relative difference of at least two-fold in expression levels, the disclosed nucleic acids and corresponding polypeptides and antibodies have utility as cancer diagnostic tools. Hu *et al.* does not support the PTO's position, and is not contrary to Applicants' asserted utility. Thus, the PTO has not offered any substantial reason or evidence to question the data in Example 18, or the first Grimaldi Declaration. In fact, in the closely related application Serial No. 10/063,688, the PTO has acknowledged that the nucleic acids encoding PRO1277 have utility.

Second, Applicants have shown that the second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in protein levels. Haynes *et al.* and Gygi *et al.* do not address this issue, and are not contrary to Applicants' asserted utility. Portions of Chen support Applicants' position, while the remainder is not contrary to Applicants' assertion that generally

there is a correlation. Thus, the PTO has not offered any substantial reason or evidence to question Applicants' declarations and supporting references.

Third, Applicants have shown that it is not necessary to know what role PRO1277 plays in cancer to use it as a diagnostic tool. The PTO's own guidelines recognize this fact, and numerous patents have issued which claim differentially expressed polypeptides and antibodies to the same, or methods employing such antibodies.

Finally, the PTO asserts that there is no asserted specific utility. Applicants have pointed out that the substantial utilities described above are specific to the claimed polypeptides because the PRO1277 gene and polypeptide are differentially expressed in certain cancer cells compared to the corresponding normal cells. This is not a general utility that would apply to the broad class of polypeptides.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed polypeptides as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing **some** beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely... A commercially successful product is not required... Nor is it essential that the invention accomplish all its intended functions... or operate under all conditions... partial success being sufficient to demonstrate patentable utility... In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed polypeptides relating to PRO1277 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO maintains its rejection of Claims 4-17 as lacking enablement. The PTO states that because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed polypeptides. Applicants respectfully request that to the extent the enablement rejection is based on a lack of utility, the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

The PTO also rejects Claims 4-6 and 12-17 under 35 U.S.C. § 112, first paragraph as lacking enablement. The PTO states that even if the specification taught how to use the PRO1277 polypeptide, enablement would not be commensurate in scope with claims 4-6, and 12-17. The PTO states:

> Applicants are not enabled for polypeptides that have at least 95-99% identity to SEQ ID NO:34 or the various fragments of SEQ ID NO:34 because there is no structural or functional information provided in the specification. In addition, the lack of direction/guidance presented in the specification regarding which variants of polypeptides of SEQ ID NO:34 would retain the desired activity, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity, the absence of working examples directed to variants and the breath of claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. *Office Action* at 14 (emphasis in original).

The PTO argues that there is no way to know which variants would have the same property of higher expression in specific tissue, stating that there is no nexus between degree of homology and regulation of gene expression. The PTO also states that similarly, there is no nexus between the degree of homology and the ability of the antibody (generated to polypeptide fragments) to specifically detect the polypeptide of SEQ ID NO:34 in esophageal and skin tissue samples. *Office Action* at 14-15.

The pending claims are to polypeptides that have at least 95% or 99% amino acid sequence identity to the recited sequences and wherein said isolated polypeptide "is more highly expressed in normal esophageal tissue or normal skin compared to esophageal tumor or

melanoma tumor respectively, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in normal esophageal tissue or normal skin compared to esophageal tumor or melanoma tumor respectively" or wherein the "isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:34 in esophageal or skin tissue samples."

As an initial matter, Applicants note that Claim 6, like Claims 7-11, does not claim polypeptides that are homologous to SEQ ID NO:34, and therefore the above arguments are not applicable to Claim 6.

In addition, Applicants submit that the claimed polypeptides are enabled, as one of skill in the art would know how to make and use them. It is well-established in the art how to make the claimed polypeptides which have at least 95% or 99% amino acid sequence identity to the disclosed sequences related to SEQ ID NO:34. Applicants have disclosed how to determine if the claimed polypeptides or encoding nucleic acids are differentially expressed in esophageal or melanoma tumors compared to normal esophageal or skin tissue. Applicants have also disclosed how to make antibodies to the polypeptide of SEQ ID NO:34, and given the high amino acid sequence homology of the claimed polypeptides, one of skill in the art would know how to make antibodies to SEQ ID NO:34 from the claimed polypeptides. Thus, one of skill in the art would know how to make the claimed polypeptides.

As discussed above, Applicants submit that they have established that one of skill in the art would believe that it is more likely than not that the PRO1277 gene and polypeptide are differentially expressed in esophageal or melanoma tumors such that they can be used as cancer diagnostic tools. Contrary to the PTO's assertions, Applicants have provided information regarding the differential expression of the PRO1277 polypeptide in cancer in the form of acceptable indirect evidence which is reasonably correlated to the asserted utility. Given the disclosure in the specification and the level of skill in the art, a skilled artisan would know how to use the claimed polypeptides as diagnostic tools. For example, polypeptides which have at least 95% or 99% amino acid sequence identity to the disclosed sequences and are "more highly expressed in normal esophageal tissue or normal skin compared to esophageal tumor or melanoma tumor respectively,..." can be used as diagnostic tools since the claimed polypeptides or their encoding nucleic acids are differentially expressed in esophageal or melanoma tumors.

Other claimed polypeptides which have at least 95% or 99% amino acid sequence identity to the disclosed sequences and "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:34 in esophageal or skin tissue samples" are also useful as diagnostic tools.

In response to the PTO's arguments, Applicants submit that based on the specification and knowledge of one of skill in the art, they have disclosed how to determine if either the encoding mRNA or the claimed polypeptide itself is more highly expressed in normal esophageal or skin tissue compared to esophageal or melanoma tumor, respectively. In addition, there is clearly a nexus between the degree of homology of the claimed polypeptides to SEQ ID NO:34 and the ability of antibodies to the claimed homologous polypeptides to specifically detect PRO1277 polypeptide in esophageal or skin tissue. The more similar the claimed polypeptides are to SEQ ID NO:34, the more likely they are to share an epitope with SEQ ID NO:34.

Given the skill in the art and the disclosure of how to make and use the claimed polypeptides, Applicants request that the PTO reconsider and withdraw its enablement rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO maintains the rejection of Claims 4-6, 12-17 under 35 U.S.C. § 112, first paragraph, as failing to satisfy the written description requirement for the reasons set forth in the previous Office Action. Briefly, the PTO asserts the Applicants were not in possession of all or a significant number polypeptides that have 95-99% homology to SEQ ID NO:34 and still retain the function of SEQ ID NO:34.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112 , first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. *See e.g.,*

Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains. The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

As amended, the pending claims are related to isolated polypeptides having at least 95% or 99% amino acid sequence identity to several polypeptides related to SEQ ID NO:34, and satisfy the limitation "wherein said isolated polypeptide is more highly expressed in normal esophageal tissue or normal skin compared to esophageal tumor or melanoma tumor respectively, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in normal esophageal tissue or normal skin compared to esophageal tumor or melanoma tumor respectively." or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:34 in esophageal or skin tissue samples."

Applicants maintain that there is no substantial variation within the species which fall within the scope of the amended claims, which require at least 95% or 99% amino acid sequence identity to the disclosed sequences related to SEQ ID NO:34. Applicants note that the pending Claims are analogous to the claims discussed in Example 14 of the written description training materials. In Example 14, the written description requirement was found to be satisfied for

claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, even though the applicant had not made any variants. Similarly, the pending claims also have very high sequence homology to the disclosed sequences and must share the same expression pattern in certain tumors, or share an epitope sufficient to generate antibodies which specifically detect the polypeptide of SEQ ID NO:34 in esophageal or skin tissue samples.

In Example 14, the procedures for making variants were known in the art and the disclosure taught how to test for the claimed catalytic activity. Similarly, in the instant application, it is well known in the art how to make polypeptides with at least 95% amino acid sequence identity to the disclosed sequences. In addition, the specification discloses how to test to determine if the polypeptide or encoding nucleic acid is differentially expressed in esophageal or melanoma tumors, and how to make antibodies which specifically detect the polypeptide of SEQ ID NO:34 in esophageal or skin tissue samples. Like Example 14, the genus of polypeptides that have at least 95% or 99% amino acid sequence identity to the disclosed sequences will not have substantial variation.

Furthermore, while Applicants appreciate that actions taken by the PTO in other applications are not binding with respect to the examination of the present application, Applicants note that the PTO has issued many patents containing claims to variant nucleic acids or variant proteins where the applicants did not actually make such nucleic acids or proteins. Representative patents submitted in the previous response include U.S. Patent No: 6,737,522, U.S. Patent No. 6,395,306, U.S. Patent No. 6,025,156, U.S. Patent No. 6,645,499, U.S. Patent No. 6,498,235, and U.S. Patent No. 6,730,502.

The PTO has responded to these arguments by stating that "even a very skilled artisan could not envision the detailed chemical structure of all or a significant number of encompassed PRO1277 polypeptides, and therefore, would not know how to make or use them." *Office Action* at 16 (emphasis added). The PTO states the Applicants made no variant polypeptides, and as recited in the current Written Description Guidelines, "Applicants must have invented the subject matter that is claimed and must be in 'possession' of the claimed genus." *Office Action* at 17.

In a recent Federal Circuit decision, *In re Wallach*, 378 F.3d 1330, 1333-34 (Fed. Cir. 2004), the Court stated:

> [W]e agree with Appellants that the state of the art has developed such that the complete amino acid sequence of a protein may put one in possession of the genus of DNA sequences encoding it, and that one of ordinary skill in the art at the time the '129 application was filed may have therefore been in possession of the entire genus of DNA sequences that can encode the disclosed partial protein sequence, even if individual species within that genus might not have been described or rendered obvious. ... A claim to the genus of DNA molecules complementary to the RNA having the sequences encompassed by that formula, even if defined only in terms of the protein sequence that the DNA molecules encode, while containing a large number of species, is definite in scope and provides the public notice required of patent applicants.
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> ***
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> Moreover, we see no reason to require a patent applicant to list every possible permutation of the nucleic acid sequences that can encode a particular protein for which the amino acid sequence is disclosed, given the fact that it is, as explained above, a routine matter to convert back and forth between an amino acid sequence and the sequences of the nucleic acid molecules that can encode it. *Id.* (emphasis added).

The Court did not require the Applicants in *Wallach* to actually make and individually describe all of the vast number of sequences which encode the disclosed sequence. This is in spite of the fact that there is no possibility that even the most skilled artisan could "envision the detailed chemical structure of all or a significant number" of encompassed polynucleotides. Because it is routine to convert between amino acid sequences to nucleic acid sequences, disclosure of a single amino acid sequence was sufficient to describe the very large genus of nucleic acids which could encode the sequence.

The facts in *Wallach* are very similar to the instant case. Here, Applicants have disclosed SEQ ID NO:34, and claim polypeptides which are homologous to it and have the functional limitation of differential expression or the ability to generate antibodies which can be used to specifically detect SEQ ID NO:34 in esophageal or skin tissue samples. It is routine in the art to create polypeptides which have at least 95% or 99% sequence identity to SEQ ID NO:34 – it is just as predictable and easy as creating all of the nucleic acids which encode a particular amino acid sequence. Similarly, it is well within the skill of those in the art to determine which polypeptides share the requisite expression patterns or can be used to make the recited antibodies. These structure/function combinations are sufficient to describe the claimed polypeptides. The

Wallach opinion makes clear that there is no need to list each individual sequence within the genus to adequately describe the genus.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO:34, by specifying a high level of amino acid sequence identity, by describing how to test for differential expression of the polypeptide and encoding nucleic acid, and by describing how to make antibodies to the disclosed sequence, all of which result in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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